ORM Pharmacology/Toxicology Senior Policy Team Meeting –Special Executive CAC
September 29, 1999

Policy Team Joseph DeGeorge, Ph.D., HFD-024, Associate Director for Pharmacology and Toxicology
Paul Andrews, Ph.D., ODE I
Dave Morse, Ph.D., ODE III
Jim Farrelly, Ph.D., ODE IV
Abby Jacobs, Ph.D., ODE V
Joseph Contrera, Ph.D., HFD-900
Jasti Choudary, B.V.Sc., Ph.D., HFD-180, Team Leader
Tim Robison, Ph.D., HFD-180, Presenting Reviewer
Adele Seifried, M.S., Executive Secretary

The following information reflects a brief summary of the Policy Team discussion and its recommendations. Detailed study information can be found in the individual review.

Drug Name: Senna (Powdered Senna Pods, purity stated at 5%; although, it was not clear how purity was defined).

Sponsor: Purdue Pharma L.P.

Background: The sponsor has proposed to conduct one carcinogenicity study with powdered senna pods that will evaluate the potential carcinogenic activity of all marketed senna products. The sponsor proposed doses of 25, 200, and 600 mg/kg/day for a 2-year carcinogenicity study in Sprague-Dawley rats based upon results from a 13-week oral dose range finding toxicology study. Rats received powdered senna pods (purity stated at 5%; although, it was not clear how purity was defined) at doses of 0, 100, 300, 750, or 1500 mg/kg/day. There was no treatment-related mortality. Body weight gains for male rats at 100, 300, 750, and 1500 mg/kg/day were 94, 96, 81.5, and 72% of the control, respectively. Body weights for female rats at 100, 300, 750, and 1500 mg/kg/day were 98, 90, 88, and 85.8% of the control, respectively. Water consumption for male rats at 300, 750, and 1500 mg/kg/ day were increased to 115, 150, and 161% of the control, respectively. Water consumption for female rats at 300, 750, and 1500 mg/kg/day were increased to 112, 145, and 165% of the control, respectively. The kidney was the target organ of toxicity. Tubular pigment deposits were observed for male rats at doses ≥300 mg/kg/day and female rats at doses ≥750 mg/kg/day. Tubular basophilia was observed for female rats at doses ≥300 mg/kg/day and male rats at doses ≥750 mg/kg/day. Changes in serum and urine electrolyte levels as well as several urinalysis parameters appeared to correlate with observed kidney lesions. Mucosal hyperplasia was observed in the cecum and colon for all male and female treatment groups. Mucosal hyperplasia was observed in the rectum for male and female rats at doses ≥300 mg/kg/day. Hyperkeratosis was observed in the stomach for all female treatment groups; although, the actual location was not specified. Squamous cell hyperplasia near limiting ridge was observed in the stomach for all male treatment groups and for female rats at 1500 mg/kg/day. The maximum tolerated dose for powdered senna pods for both male and female rats appears to be between 300 and 750 mg/kg/day.

ORM Pharmacology/Toxicology Senior Policy Team Recommendations and Conclusions:

1. The committee recommended doses of 300, 100, and 25 mg/kg/day for the 2-year rat carcinogenicity study, based upon renal lesions observed at doses ≥ 300 mg/kg/day in the dose range finding study.

2. The observed toxic effects in 13-week oral dose range finding studies with powdered senna pods (Purdue Frederick Labs of Totowa, New Jersey) and sennoside extract (Novartis Consumer Health of Switzerland) appeared identical based upon histopathology findings of renal lesions and mucosal hyperplasia in the cecum, colon, and rectum. The differences in doses are probably related to concentrations of the active moieties.

3. The results of this rat carcinogenicity study will be considered generally representative of marketed pharmaceutical senna products.

78N-036L

MM18

4. The study protocol for the 2-year carcinogenicity study in Sprague-Dawley rats appears acceptable assuming that doses are changed as noted under #1. Drug will be administered by oral gavage. Histopathological analysis of major organs and tissues in all animals is acceptable. Full histopathological analysis should be also performed with all animals that die or are sacrificed in a moribund condition during the treatment period.

5. The definition and basis of "purity" of the powdered senna pods in the 13-week dose range finding study as well as the 2-year rat carcinogenicity study should be provided. The definition and basis of "purity" of the sennoside extract in the 13-week dose range finding study should also be provided.

6. The sponsor(s) should consider obtaining pharmacokinetic data from human subjects following oral administration of senna for comparison with toxicokinetic data obtained from rats to facilitate interpretation of any tumor findings.

10/13/99

Joseph DeGeorge, Ph.D.
Associate Director for Pharmacology and Toxicology

cc:
Division File, HFD-560
Cheryl Turner, R.N., HFD-560
Jasti Choudary, B.V.Sc., Ph.D., HFD-180
Timothy Robison, Ph.D., HFD-180
Adele Seifried, HFD-024

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: Nov. 8, 1999

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 78N-036L.

TO: Dockets Management Branch, HFA-305

☒ The attached material should be placed on public display under the above referenced Docket No.

☐ This material should be cross-referenced to Comment No. _____

Charles J. Ganley, M.D.

Attachment